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Food and Drug Administration
Department of Health and Human Services
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Rockville, MD 20852

CITIZEN PETITION

This petition is submitted on behalf of GlaxoSmithKline ("GSK") pursuant to 21 CFR §10.30. GSK requests the Commissioner of Food and Drugs to remove metered-dose inhalers ("MDIs") containing the single active moieties beclomethasone, fluticasone, and salmeterol, respectively, from the essential-use list of ozone-depleting substances ("ODS") set forth in the Food and Drug Administration's ("FDA") regulation of such substances.¹ As discussed below, because the legal and factual predicates for this action are not in dispute, GSK requests that FDA: (a) take this action via a direct final rule; (b) that it do so prior to the rulemaking discussed at the July 14, 2005 meeting of Pulmonary-Allergy Drugs Advisory Committee ("PADAC");² and (c) that the effective date of the action be no more than 30-days after publication of the final rule.

A. ACTION REQUESTED

For the reasons discussed in section B, this petition requests the Commissioner to amend 21 CFR § 2.125(e)(1)(i), 21 CFR § 2.125(e)(1)(iv) and 21 CFR § 2.125(e)(4)(i) to read as follows:

¹ The essential-use list is set forth in 21 CFR § 2.125(e)(1). *See also Use of Ozone-Depleting Substances; Essential-Use Determinations*, 67 Fed. Reg. 48370, 48373 (July 24, 2002) (final rule) (hereinafter "ODS Regulation").

² *See* Transcript of July 14, 2005 PADAC Meeting; statement of Wayne Mitchell at 33-35, *available at* <<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4148T2.htm>>.

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CP1

(1) *Metered-dose corticosteroid human drugs for oral inhalation.* Oral pressurized metered-dose inhalers containing the following active moieties:

- (i) [Removed and Reserved].
- (ii) Dexamethasone.
- (iii) Flunisolide.
- (iv) [Removed and Reserved].
- (v) Triamcinolone.

...

(4) *Other essential uses.*

- (i) [Removed and Reserved].

....

B. STATEMENT OF GROUNDS

Under 21 CFR § 2.125(g)(1), FDA may remove an essential use from the list at 21 CFR § 2.125(e) if the product using the ODS is no longer being marketed. In its ODS Regulation, FDA stated that the “failure to market indicates nonessentiality because the absence of a demand sufficient for even one company to market the product is highly indicative that the use is not essential.”³ Chlorofluorocarbons (CFC) MDIs containing the single active moieties beclomethasone, fluticasone, and salmeterol, respectively, are no longer being marketed; thus, the sole criterion required by FDA to de-list beclomethasone, fluticasone, and salmeterol from 21 CFR § 2.125(e) has been met.⁴

1. *The Sole Regulatory Criterion for De-Listing Has Been Met*

a. Beclomethasone

Until recently, beclomethasone was marketed as an ODS product represented by two distinct new drug applications. The CFC beclomethasone MDIs on the market were Vanceril[®] (“Vanceril CFC”) and Beclovent[®] (“Beclovent CFC”), each of which was marketed under its own new drug application (NDA 17-573 and NDA 18-153, respectively).⁵ Schering-Plough

³ See ODS Regulation at 48373

⁴ 21 CFR § 2.125(g)(1). The MDIs that this petition seeks to de-list all contained CFC 11 and CFC 12, which are ODS controlled under the Clean Air Act. See 42 USC § 7671a(a); see also 40 CFR Part 82, Subpart A, Appendix A.

⁵ See NDA # 17-573 and NDA # 18-153, respectively. The active moiety in both Vanceril CFC and Beclovent CFC was beclomethasone propionate.

Corporation (“Schering-Plough”) introduced Vanceril CFC into the U.S. market, after obtaining U.S. approval for the drug in 1982.⁶ GSK introduced Beclovent CFC into the U.S. market, after obtaining U.S. approval for the drug in 1982.⁷ Vanceril CFC and Beclovent CFC both contained CFC 11 and 12.

3M Pharmaceuticals developed a non-ODS beclomethasone MDI product – QVAR[®] HFA, represented by a single new drug application (NDA 20-911) – which was approved by FDA in 2000.⁸ IVAX Corporation is currently marketing QVAR[™] HFA in the United States.⁹ GSK ceased manufacturing Beclovent CFC in the United States in 2001. By 2003, GSK had sold all remaining Beclovent CFC in inventory, and thus by that time had ceased not only manufacturing, but also all commercial distribution in the United States.¹⁰ With respect to Vanceril CFC, FDA has determined that Schering-Plough is no longer marketing this product in the U.S. market.¹¹

Vanceril CFC and Beclovent CFC were the only CFC beclomethasone MDI products on the market in the United States. Thus, with the cessation of manufacture and commercial distribution in the United States by Schering-Plough and GSK, respectively, there are no CFC beclomethasone MDI products on the U.S. market.¹²

b. Fluticasone

Until recently, fluticasone¹³ was marketed as an ODS product – Flovent[®] (fluticasone propionate) Inhalation Aerosol (“Flovent CFC”) – represented by a single new drug application

⁶ See NDA # 17-573.

⁷ See NDA # 18-153.

⁸ See NDA # 20-911.

⁹ See Letter from IVAX Corporation to Shareholders (Feb. 2, 2005), available at <http://www.ivax.com/pdfs/shareholder_letter_february_02_05.pdf>.

¹⁰ See *Withdrawal of Approval of 80 New Drug Applications*, 68 Fed. Reg. 49481, 49484 (August 18, 2003) (notice) (withdrawing FDA approval of Beclovent CFC’s NDA # 18-153 on the basis that Beclovent CFC is no longer marketed in the United States).

¹¹ See Dep’t of Health and Human Servs., Food and Drug Administration, *Approved Drug Products, Cumulative Supplement 9* (25th ed. Sept. 2005), available at <<http://www.fda.gov/cder/orange/obcs.pdf>> (hereinafter “*Orange Book*”). In the *Orange Book*, Vanceril CFC is listed as “discontinued”. See *id.* at 1-9. According to the *Orange Book*, a product is considered to be “discontinued” if it “is not being marketed” See *id.* at ix.

¹² See *id.* at 1-9. In the *Orange Book*, under the active ingredient beclomethasone, Vanceril is the only product listed. As stated above, the *Orange Book* lists Vanceril as “discontinued” – i.e., not marketed in the United States. See *supra* note 11.

¹³ The individual active moiety in Flovent CFC is fluticasone propionate. Please note, however, that the general term “fluticasone” appears in FDA’s essential-use list. See 21 CFR § 2.125(e)(1)(iv)

(NDA 20-548).¹⁴ GSK introduced Flovent CFC into the U.S. market, after obtaining U.S. approval for the drug in 1996.¹⁵ Flovent CFC contained CFC 11 and 12. GSK later developed a non-ODS fluticasone MDI product – Flovent HFA[®] (fluticasone propionate) Inhalation Aerosol, represented by a single new drug application (NDA 21-433) – which was approved by FDA in May 2004.¹⁶ GSK launched Flovent HFA in February 2005. Consistent with the Montreal Protocol¹⁷ and Title VI of the Clean Air Act regarding the phase-out of production and consumption of ODS, GSK ceased manufacturing Flovent CFC in the United States in November 2004. GSK has no remaining Flovent CFC in inventory and has completely ceased commercial distribution of this product in the United States.

Flovent CFC was the only CFC fluticasone MDI product on the market in the United States;¹⁸ with the cessation of manufacture and commercial distribution in the United States by GSK, there are no CFC fluticasone MDI products on the U.S. market.

c. Salmeterol

Until 2002, salmeterol was marketed as an ODS product – Serevent[®] (“Serevent CFC”) – represented by a single new drug application (NDA 20-236).¹⁹ GSK introduced Serevent CFC into the U.S. market, after obtaining U.S. approval for the drug in 1994.²⁰ Serevent CFC contained CFC 11 and 12. GSK later developed a non-ODS salmeterol product – Serevent Diskus[®] (salmeterol xinafoate inhalation powder), represented by a single new drug application (NDA 20-692) – which was approved by FDA in 1997.²¹ GSK ceased manufacturing Serevent CFC in the United States in January 2003. By June 2003, GSK had depleted all remaining Serevent CFC in inventory, and thus by that time had ceased all commercial distribution of this product in the United States.

¹⁴ See NDA # 20-548.

¹⁵ See *id*

¹⁶ See NDA # 21-433.

¹⁷ The Montreal Protocol on Substances that Deplete the Ozone Layer, an international treaty to which the United States is party, mandates the phase-out of ODS production and importation. See *Montreal Protocol on Substances that Deplete the Ozone Layer*, S. Treaty Doc. No. 10, 100th Cong., 1st sess., 26 I.L.M. 1541 (1987), available at <<http://www.unep.org/ozone/pdfs/Montreal-Protocol2000.pdf>>.

¹⁸ See *Orange Book* at 1-34. In the *Orange Book*, as of August 2005, Flovent CFC is shown as the only CFC fluticasone MDI product in the U.S. market.

¹⁹ See NDA # 20-236.

²⁰ See *id*

²¹ See NDA # 20-692.

Serevent CFC was the only CFC salmeterol MDI product on the market in the United States; with the cessation of manufacture and commercial distribution in the United States by GSK, there are no CFC salmeterol MDI products on the U.S. market.²²

2. *Public Benefits of Action*

Removing CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the essential-use list serves the best interests of the public in three ways: (i) improved public awareness that CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs are no longer marketed in the United States and that CFC-free alternatives are available; (ii) continued health benefits from prevention of future depletion of the ozone layer; and (iii) bolstered support among the Montreal Protocol Parties for U.S. efforts to further the transition.

Regarding the first public benefit, GSK recognizes that it has the primary responsibility to inform the healthcare community of the cessation of sales of GSK's CFC MDI products, the reasons for such cessation, and the availability of non-CFC alternatives. Consequently, when GSK suspended its sales of Beclovent CFC, Flovent CFC, and Serevent CFC, it took several actions to notify the affected public of such suspensions.²³ Nevertheless, despite these public announcements and other actions, there may be some residual confusion in the market place – particularly among physicians and patients – as to the current availability of CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs.²⁴ Publication of a final rule removing these CFC MDI products from the essential-use list will help spread the word throughout the healthcare community, and thus help to alleviate any remaining confusion in the market.

Second, removing CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the essential-use list serves the best interests of the public by continuing the health benefits already achieved from reduced depletion of the ozone layer. Because these products are no longer being marketed, their combined harm to the stratospheric ozone is minimal or none. Removing these CFC MDI products from the essential-use list will help ensure that this status is not reversed in the future.

²² See *Orange Book*. In the *Orange Book*, as of August 2005, no CFC salmeterol MDI products are listed as being sold or distributed in the U.S. market.

²³ See e.g., press release, GlaxoSmithKline, Ozone Friendly formulation, *Flovent* HFA (Fluticasone Propionate HFA) Inhalation Aerosol, Now Available (Feb. 7, 2005) available at <<http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsId=407>>.

²⁴ For example, GSK has received, and continues to receive, numerous inquiries from physicians and patients as to the availability of Serevent CFC.

Third, the international community's patience with the pace of the United States' CFC MDI products phase-out has been wearing thin in recent years.²⁵ Removing CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the essential-use list will send a positive message to the international community that the United States is committed to transitioning away from ODS use in medical products and to protecting the ozone layer.

3. *Request for Action as Direct Final Rule*

As stated above, there is no dispute that the sole requirement for removal of CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the FDA's essential-use list is whether these products are still being marketed. Further, the fact that these CFC MDI products are no longer being marketed is not in question. Thus, there is no issue of law or fact in dispute. Accordingly, FDA may remove beclomethasone, fluticasone, and salmeterol from the essential-use list without first publishing a notice of proposed rulemaking and soliciting public comments.

Under FDA regulations at 21 CFR § 10.40(e)(1), "[t]he requirements of notice and public procedure . . . do not apply . . . [w]hen the Commissioner determines for good cause that they are . . . unnecessary"²⁶ This FDA exemption mirrors a similar exemption in the Administrative Procedure Act ("APA").²⁷ When enacting the APA exemption, Congress stated that the "lack of public interest in rule-making warrants an agency to dispense with public procedure."²⁸ Here, where there is no question of law or fact in dispute, the Commissioner may dispense with advance notice and opportunity for comment. Therefore, GSK requests that FDA effect the removal of beclomethasone, fluticasone, and salmeterol from the essential-use list by direct final rule.

4. *Request for Earlier Rulemaking*

In addition, GSK requests that FDA issue a direct final rule prior to issuing the proposed rule contemplated at the July 14, 2005 PADAC Meeting. At that meeting, FDA discussed issuing a proposed rule to remove other CFC MDIs from the essential-use list: specifically, CFC

²⁵ See, e.g., Transcript of June 10, 2004 PADAC Meeting; statement of Eugene Sullivan at 56-57, available at <<http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4048T1.htm>> (stating that Parties to the Montreal Protocol may not continue to accept United States' claim of "essentiality" of certain CFC MDI products). See also 2005 TEAP Report, which recommends a substantially reduced quantity of authorized essential use volumes for the U.S. for 2006. See United Nations Environment Programme, Report of the Technology and Economic Assessment Panel at 38-41 (May 2005).

²⁶ 21 CFR § 10.40(e)(1).

²⁷ See Administrative Procedure Act, 5 USC § 553(b)(B).

²⁸ See S. Doc. No. 248, 79th Cong., 2d Sess. at 200 (1946).

MDIs containing metaproterenol, pirbuterol, flunisolide, triamcinolone, cromolyn, nedocromil and albuterol/ipratropium, respectively (hereinafter the “PADAC CFC MDIs”).²⁹ However, the PADAC CFC MDIs are distinguishable from CFC MDIs containing beclomethasone, fluticasone, or salmeterol in that: (1) the PADAC CFC MDIs are all still being marketed in the United States; (2) there are “no non-CFC current reformulations or direct alternative products” for the PADAC CFC MDIs;³⁰ and (3) the PADAC CFC MDIs would be removed from the essential-use list pursuant to a different section of the ODS Regulation – 21 CFR § 2.125(g)(2), rather than 21 CFR § 2.125(g)(1). To remove products from the essential-use list under 21 CFR § 2.125(g)(2), FDA is required to assess whether the multiple fact-based criteria set forth in 21 CFR § 2.125(f) have been met for *each* of the seven PADAC CFC MDIs. By contrast, de-listing under 21 CFR § 2.125(g)(1) requires only a finding that the CFC MDI product is no longer on the market.

Thus, consolidating these two distinct rulemaking processes could unnecessarily delay the removal of CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs, and possibly slow down FDA action on the PADAC CFC MDIs. Accordingly, GSK requests that, prior to issuing a proposed rule concerning the PADAC CFC MDIs, FDA issue a direct final rule to remove CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the essential-use list.

5. *Request for Effective Date 30 Days After Publication*

GSK requests that the Commissioner make the direct final rule effective 30 days after publication. Under FDA regulations at 21 CFR § 10.40(c)(4), “[t]he effective date of a final regulation may not be less than 30 days after the date of publication in the Federal Register”³¹ Unlike the prior de-listing instances, there is no reason to delay the effectiveness beyond the required 30 days.

In its final rule removing CFC albuterol MDIs from the essential-use list, FDA set an effective date more than three years after the final rule publication date.³² However, in that case, FDA stated that it delayed the effective date in order to ensure that adequate production capacity and supplies be in place to serve the entire albuterol MDI market.³³ Although the sufficiency of the supplies and production capacity is one of the criteria for removal under 21 CFR

²⁹ See July 14, 2005 PADAC Meeting at 85-132.

³⁰ Memorandum from Robert J. Meyer, Director, to PADAC (July 5, 2005), available at <http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4148B2_01_FDA-Office-DIR-Memo.pdf>.

³¹ 21 CFR § 10.40(c)(4).

³² See *Use of Ozone-Depleting Substances, Removal of Essential-Use Designations* 70 Fed. Reg. 17168, 17178 (Apr. 4, 2005) (final rule) (hereinafter “CFC Albuterol Non-Essentiality Rule”).

³³ See *id*

§ 2.125(g)(4),³⁴ it is not a criterion for de-listing pursuant to 21 CFR § 2.125(g)(1). CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs are currently not marketed in the United States, which means, in FDA's own words, that there is an "absence of a demand sufficient for even one company to market the product."³⁵ Thus, there is no need to provide phase-out periods for CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs in order to ramp up production capacity for the non-CFC alternatives to these products.

Similarly, when it removed CFC-containing metered-dose steroid nasal inhalants from the essential-use list, FDA delayed applicability by one year. In that case too, the CFC nasal steroid MDIs were still being marketed in the United States. Because of that fact, FDA concluded that "a 1-year period to dispose of existing stocks and to complete the transition to non-ODS-containing alternatives [would be] appropriate."³⁶

The only other prior instance to date of de-listing was FDA's action on CFC MDIs containing isoetharine, isoproterenol and terbutaline, respectively. These CFC MDIs were removed because, as is the case here, they were no longer being marketed in the United States. FDA effected the de-listing of these three active ingredients as part of its promulgation of the ODS Regulation. The ODS Regulation not only removed the CFC isoetharine MDIs, CFC isoproterenol MDIs and CFC terbutaline MDIs from the essential-use list, but it also implemented several new criteria and procedures for additions to and removals from the essential-use list. Because the effective date of the ODS Regulation was 180 days after the publication date,³⁷ FDA also set a 180-day delay in effectiveness for the removal of these active ingredients. By contrast, in this instance, other than the simple removal of CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the essential-use list, there would be no other amendments to the ODS Regulation. Therefore, GSK requests that FDA make the direct final rule effective immediately after 30 days from its publication.

D. ENVIRONMENTAL IMPACT

21 CFR § 10.30 requires the petitioner to prepare an environmental assessment under 21 CFR § 25.40. However, an environmental assessment is not necessary here. 21 CFR § 25.40 defines environmental assessment as "a concise public document that serves to provide sufficient evidence and analysis for an agency to determine whether to prepare an [environmental impact statement] or a [finding of no significant impact]."³⁸ The environmental assessment fulfills

³⁴ See 21 CFR § 2.125(g)(4).

³⁵ See *ODS Regulation* at 48373.

³⁶ *Id.* at 48375.

³⁷ See *id.* at 48372.

³⁸ 21 CFR § 25.40; see also 40 CFR § 1508.9.

FDA's obligations under the National Environmental Policy Act of 1969 ("NEPA").³⁹ NEPA requires all federal agencies to assess the environmental impact of their actions "significantly affecting the quality of the human environment."⁴⁰ However, Federal agency actions taken under the Clean Air Act are deemed by Federal law not to have any significant environmental impact.⁴¹ FDA actions to de-list an essential use are taken pursuant to the agency's authority under the Clean Air Act.⁴²

In any case, the removal of beclomethasone-, fluticasone- and salmeterol-containing CFC MDIs from the essential-use list will not in fact have a significant adverse impact on the human environment. To the contrary, it will maintain, and indeed make irreversible, the current benefits to the environment derived from the unavailability of ozone-depleting substances in drug products containing these three active ingredients. Thus, an environmental assessment is not required.

D. ECONOMIC IMPACT

Pursuant to 21 CFR § 10.30, information under this section is to be submitted only when requested by the Commissioner following review of the petition.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

³⁹ See Environmental Impact Statements, 38 Fed. Reg. 7001 (Mar. 15, 1973), *amended by* 42 Fed. Reg. 19986 (Apr. 15, 1977) and 50 Fed. Reg. 16636 (Apr. 26, 1985).

⁴⁰ 42 USC § 4332.

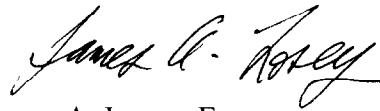
⁴¹ See 15 USC § 793(c)(1).

⁴² See *ODS Regulation*, 67 Fed. Reg. at 48370, 48371, 48381, 48382.

F. CONCLUSION

For the foregoing reasons, GSK requests that this petition be granted, and that FDA issue a direct final rule, which would take effect 30 days after publication, to remove CFC beclomethasone MDIs, CFC fluticasone MDIs, and CFC salmeterol MDIs from the essential-use list at 21 CFR § 2.125(e)(1)(i), 21 CFR § 2.125(e)(1)(iv) and 21 CFR § 2.125(e)(4)(i), respectively.

Respectfully Submitted,

A handwritten signature in cursive script, appearing to read "James A. Losey".

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